New Perspectives on the Causes and Potential Costs of Malaria:

The Growth and Development of Children. What Should We be Measuring and How Should We be Measuring It?

DISEASE CONTROL PRIORITIES PROJECT

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DISEASE CONTROL PRIORITIES PROJECT

BACKGROUND

In the late 1980s, the World Bank initiated work to inform priorities for control of specific diseases and to generate comparative cost-effectiveness estimates for interventions addressing the full range of conditions important in developing countries. The purpose of the comparative cost-effectiveness work was to provide one input into decision-making within the health sectors of highly resource-constrained countries. This process resulted in the 1993 publication of *Disease Control Priorities in Developing Countries**. A decade after publication of the first edition, the World Bank, the World Health Organization, and the Fogarty International Center (FIC) of the U.S. National Institutes of Health (NIH) have initiated a "Disease Control Priorities Project" (DCPP) that will, among other outcomes, result in a second edition of *Disease Control Priorities* in Developing Countries (DCP*2*). The DCPP is financed in part by a grant from the Bill & Melinda Gates Foundation. DCP*2* is intended both to update DCP*1* and to go beyond it in a number of important ways, e.g. in documentation of success stories, in discussion of institutional and implementation issues, and in explicit discussion of research and development priorities. Publication of DCP*2* is intended for mid-2005.

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Abstract

There are a number of pathways, both direct and indirect, through which malaria infection could impact on the course of child development, causing impairment and disability and adding to the burden of malaria. We present an overview of relevant studies which illustrate these pathways, updating the evidence previously presented.[1] Before the mechanisms and numbers of affected children can be defined, a wider range of potential pathways to impaired development need to be investigated. Only then can the calculation of the burden be evidence-based, rather than merely speculative. The calculation of the impact of malaria on child development requires a degree of uniformity across studies in the definition of outcome following malaria infection. Suggestions are made in this article to improve reporting of results, and for priorities for future research

New Perspectives on the Causes and Potential Costs of Malaria: The Growth and Development of Children. What Should We be Measuring and How Should We be Measuring It?

Penny A. Holding, P.K. Kitsao-Wekulo

Introduction

New data looking at the association between malaria infection and learning in childhood reflects the growing recognition of the importance of the "growth and development" burden of malaria.[2,3,4] There are still very few studies, and possible pathways remain under-investigated.

In addition to the lack of data, there is an inherent variability in the methodology applied to measure developmental outcome. This limits the ability to combine results from different studies and draw general conclusions. Unlike outcome measures used in health research such as death and disease rates, applicable measures of development vary across ages, gender, cultural and linguistic groups. Selection of measures partly depends upon the age of the children being studied, because a child of 3 years cannot complete the same tasks as a child of 10. The content of tasks and questionnaires has to be selected according to the images, words and materials that are familiar to the population being tested. Even the way children respond to questions posed by adults varies markedly from one community to another, necessitating changes in procedure. Different studies need to apply different assessment tools, depending on their target population. Even when the same tool is used, no assumptions can be made that the same neuropsychological function is being measured.[5,6]
We have applied a classification system (The International Classification of Functioning, Disability and Health) (ICF)[7] to combine within one framework the outcomes identified from different studies. Wherever possible, we have used the evidence of recently published studies to update our previous description of the pathways to impairment. We have used this overview to identify important topics for future research (What should we be measuring?) and to highlight methodological issues that need to be addressed in future studies (How should we be measuring it?). Answers to these two questions are important in the identification of priority areas for intervention to reduce the burden of malaria on child growth and development.

Materials And Methods

Classification of impairments

The first tier of the ICF is “Impairment of Body Functions and Body Structures”. This is defined as a significant deviation or loss of body function or structure in the functional areas summarized in Figure 1. Analysis at this level of classification can provide information on the causal pathways of disability, and the degree of impairment. The second tier, also summarized in the same figure, is “Activity Limitations and Participation Restriction”. This refers to the ability of an individual to lead a normal life. It explains the relevance of the impairment to the individual concerned. To apply the second tier, a detailed understanding of the context in which the child lives is required. (It is not sufficient to say that the child’s memory, speech or gait is impaired to understand how this might impact on their functioning in every day living).

Knowledge of parental perceptions of a child’s difficulties, and of community expectations is essential to make an evaluation of disability. In practice, access to ethnological knowledge about specific communities is limited, either because it has not been published alongside research data, or because it has not been collected. Research needs to accord greater importance to evaluating the ability of children to meet the demands of everyday living before there is sufficient data to complete the “Activity Limitations and Participation Restriction” tier. Our summary will therefore be restricted to classification at the first tier of the ICF.

Pathways to impairment

Figure 2 describes the pathways to impaired growth and development first identified by Holding & Snow. [1] Represented are the approximately 50% of any 1,000 children and young people in a meso-endemic transmission area who carry malaria parasites. In 400 individuals, infection will be asymptomatic. Ninety eight will have symptomatic infection of a mild nature and only 2 will have severe disease. The figure illustrates that malaria parasites are likely to exert both direct and indirect effects upon child development and functioning. The impaired outcomes that have been associated with each of the pathways are summarized in turn. For some we have to resort to drawing inferences from related diseases. Summaries based on such inferences will be reported in italics.

Results

Parasitization

A range of functional areas: learning, fine motor, cognition, and physical growth, have been investigated in relation to parasite load and clearance.[2,8,9,10] With limited studies to draw from, our conclusions are tentative, but suggest that the association varies by age and level of transmission.

In school-age children, short term parasite clearance has been associated improved performance on fine motor and memory tasks.[2] The mechanism for impairment is not clear, but may be through an alteration of attention levels.[11] Longer term follow-up is needed to establish whether benefits can be maintained over time. However, the cost of extended intervention programs, and the associated risks of the development of drug resistance, suggests that selecting school-age children as targets for chemoprophylaxis has limited efficacy .[12]

Classification of impaired outcomes

- Mental Functions[2]
- Movement related functions[2]
- Functions of the digestive, metabolic and endocrine systems [9,10]
- Structures Related to Reproductive System[14,15]

Of greater interest are the benefits of chemoprophylaxis in the first few years of life on physical growth and the development of mental functions. The early years are critical for brain growth and for development of functional immunity to malarial disease. Intervention studies in this age group may positively control the potential effects of parasitization and reduce the numbers of children who develop severe disease. Benefits may come from being a more attentive and alert child,[11,13] and from avoiding exposure to brain insult and the associated risk of developing neuro-cognitive sequelae. The effect of chemoprophylaxis in infancy on cognitive abilities 12 years later has been investigated in the Gambia. Data is currently being analyzed (Jukes, Pinder, Walraven et al. in preparation).

Investigation of impaired development following exposure to parasites in-utero, has largely focused on the indirect effect of placental parasitemia on birth outcome. Congenital malaria is potentially a more direct pathway to impairment, although it is thought to be relatively uncommon.[14] However, peripheral parasitemia, significantly associated

with anemia in infancy, has been recorded in 42% of newborns tested.[15] It is further suggested that early exposure to malaria may be related to a retarded development of natural immunity.[16]

Mild malaria and the activation of an immune response

Potential outcomes are suggested by the association found with other mild diseases between the activation of the immune response system, suppression of appetite, and reduction in the speed of reaction time (the speed with which decisions and responses are made).[17] However, these effects are likely to be very short term. In childhood they may have a longer- term effect on activity and participation if a child experiences regular episodes. Also to be determined is the definition regular, and the effect of age at onset or the length of the period of ill-health.

Classification of impaired outcomes

- Functions of the digestive, metabolic & endocrine systems
- Mental Functions

We suggest that the control of malarial disease in school age children is not an important target area for extended intervention programs because it accounts for only 3 – 8% of all absences from school.[12] Previous chemoprophylaxis programs in school children have had limited impact on attendance levels and disease incidence.[18,19] Short term programs with specific targets within the school-age population may have more visible benefits, for example in epidemic areas to reduce the risk of developing severe disease, and during national examinations, especially where the examinations coincide with seasonal peeks in malaria infection rates.[20] More needs to be known of the impact of disease on performance before such a program can be recommended.

The overwhelming burden of disease is carried by the under fives. Intervention studies aimed at reducing the burden in this age group should not only evaluate the potential benefits in improved growth and development, but also monitor the risk of changing the age profile of disease.[21] Although there is increasing evidence that protection from disease in early childhood does not cause an increase in the disease burden in older children (Slutsker L. and others, unpublished data), until the relationship between early protection and the development of natural immunity is better understood, it would be prudent to continue to monitor for the possibility of changes in disease profile.

Severe disease and brain damage

Of the two major manifestations of severe disease, severe malarial anemia and cerebral malaria, it is only the association between cerebral malaria and impaired growth and development that has been investigated. Gross neurological sequelae on discharge have been widely documented (see summary in Holding and Snow[1]). There are still only four published studies of neuropsychological consequences.[3,22-24] In common with other childhood encephalopathies, the general conclusion can be drawn that the more severe the illness, the more generalized and long term are the impairments.[25] Using the ICF[7] to summarize the results across these studies, two themes worthy of further investigation are suggested. The first concerns with the identification of similarities between study outcomes. Two functional areas, attention[3,21,22] and motor development,[22,23] are identified as the more common sequelae, and future investigations should monitor performance in these areas.

Classification of impaired outcomes

- Mental functions [3, 22-24]
- Sensory functions [23]
- Voice and speech [28]
- Movement related functions [22,23]
- Structure of the nervous system [1,23]
- Structure of the eye [48]
- Structure related to movement

The second theme to emerge is the need to explain the variability in outcome observed both between and within studies. The exact function(s) that are impaired will depend on the stage of brain growth at which the insult is encountered.[26,27] Impairment may be attributable either to identifiable lesions, or to the subsequent interference in the development of neuronal systems in the brain. Complex, higher order functions, which require more intricate systems, may be more vulnerable. A detailed study of the relationship between age of insult and outcome, which may be able to tease out some of these issues, is yet to be carried out.

Another explanation for the variability observed may be that the term 'cerebral malaria' has been used to combine children who have experienced different patho-physiological mechanisms. The investigation of one potential sub-group, children with malaria and seizures, indicates that severe impairment can follow less severe disease when underlying brain pathology (i.e. epileptic activity) continues beyond the illness episode.[28] Defining other sub-groups is a priority for the greater understanding of outcome following cerebral malaria.

A major contributor to variability in outcome will be the additional risk factors that individual children encounter. Some risk factors may have

a synergistic relationship with malarial disease, and other variables may either provide protection against severe sequelae. Maternal literacy, for example, has beneficial effects on children's general health and well being.[29] While school attendance is associated with superior performance on neuropsychological tests,[30] the difference between schooled and unschooled children has been found to be even greater in those who have experienced cerebral malaria compared to those who have not (Holding and others submitted). One causal factor might be that education contributes to resiliency in the face of adverse experiences.[31] The inter-relationship between risk factors and factors which might attenuate those risks is itself complex.[32] Understanding the relationship is important in calculating the persistence of an impairment, and in planning successful intervention programs.

Care of sick individuals

Malaria disease in the family may reduce access to education and thus employment opportunities for children who are not themselves infected. It is not known how much of the 92% plus of school days lost to causes other than direct malaria infection are spent taking care of sick siblings.[12] The temporary interruption of school attendance may disrupt the development of literacy skills. Schooling may cease altogether due to the financial burden of treatment costs for sick individuals, severely limiting the family's ability to support the continued education of all its eligible members.[33,34,35]

Classification of impaired outcomes

- Mental Functions

Nutritional status and malarial infection

Infection with both P. falciparum and P. vivax has been associated with impaired physical growth in children.[36-40] The direction of this association appears to be two-way, malaria leading to compromised nutritional status and compromised nutritional status leading to malaria infection. Catch-up growth has been observed following interventions focusing on disease prevention,[9] suggesting that malaria infection plays a role in the etiology of malnutrition, and the downward cycle of impaired development of mental functions.[41,42] Whether poor nutritional status protects or predisposes a child to developing further infection remains under debate.

Earlier studies suggested that protein energy malnutrition may be protective against malaria related morbidity and mortality.[43-45] There is increasing evidence from larger scale studies that a compromised diet at both the macro and micro nutrient level may actually increase the risk of developing disease and/ or a range of impaired outcomes.[46 -49] The debate continues, with more recent-counter evidence to the picture of a synergistic relationship between malarial disease and malnutrition showing an apparent protective effect of stunting[50] and low body mass index.[51]

Although the relationship between nutritional status and malaria infection is complex the nature of the relationship can be reduced to two essential pathways, the modulation of the immune system and alterations to oxidative stress. Investigations of the relationship between nutritional status and malaria disease have concentrated on those nutrients which may have a significant impact on either pathway. Deficiencies in some of these nutrients may also directly impact on the growth and development burden. For example, supplementation of children with vitamin A, zinc, and protein rich foods have been associated with improved performance in mental functions, social and emotional development and physical growth. [52-56]

The role of iron is more contentious, both in relation to malaria infection, and to impaired cognition.[57-62] A significant association has been established between malaria infection and the development of anemia,[63, 64] although not iron deficiency anemia. As it is specifically iron deficiency anemia that has been associated with impaired mental functions,[65-69] the same association may not be seen with malarial anemia. Iron supplementation of a malaria exposed population may still have a role to play in reducing the burden of malaria disease, if careful account is taken of the particular combination of disease risk to which the population is exposed[58,70-72] This premise holds true for other areas of nutrition.[73]

There is a growing body of evidence, carefully summarized in Shankar[73] and Nusssenblatt and Semba,[74] supporting those who advocate combination therapies of micro (and macro) nutrient supplementation and anti-malarials for the treatment and prevention of mild and severe

Classification of impaired outcomes

- Functions of the digestive, metabolic and endocrine systems [9, 36 - 40]
- Sensory functions [48]
- Immunological and Cardiovascular Systems [99]
- Movement related functions [73]
- Mental functions
- Structure of the nervous system
- Structure related to movement further infection remains under debate.

disease. Again the potential benefits appear to vary depending upon the age and immune status of the population being studied, and the level and nature of the nutritional deficit.

Fetal exposure to malaria

Maternal malaria infection in pregnancy has a well documented association with impaired outcome for the fetus, including intra uterine growth retardation (IUGR) and premature delivery (PTD), both culminating in low birth weight.[75-79] Low birth weight is a risk factor for a range of impaired outcomes, including brain injury, which can persist into adulthood.[80,81] With over 1 million babies born low birth weight in Sub Saharan Africa every year, and with estimates of malaria accounting for up to 40% of these births,[82] this pathway to impairment is potentially a major contributor to the burden of malaria disease. The most vulnerable are the children of primigravidae, as over 60% of their mothers will have been infected with malaria (compared to approximately 30% in later pregnancies).[78,83]

Classification of impaired outcomes

- Functions of the digestive, metabolic and endocrine systems[75 - 79]
- Mental functions
- Sensory functions
- Movement related functions
- Immunological, Cardiovascular and Respiratory Systems

Maternal malaria infection, in compromising fetal growth, may lead to impaired development of the central nervous system, and to subsequent impairment of mental, motor and sensory functions of the newborn.[84,85] These impairments may ultimately lead to long-lasting and wide reaching limitations in daily living. Utero placental insufficiency in non-malarial populations has been associated with the etiology of cerebral palsy, and with white matter damage.[84,86,87] Further evidence suggests that impairments in cardiovascular and respiratory structures may also have long term health implications for these children.[88,89]

Fetal growth retardation might not be the only pathway to impairment. Another mechanism for poor outcome might be intrauterine infection. Placental cytokine changes have been recorded with maternal malaria infection.[90] If a fetal inflammatory response, with corresponding changes in cytokine levels in amniotic fluid or newborn blood, is stimulated, then brain damage and neurodevelopmental disability in the child may follow.[85,91]

Sub-optimal growth and development may also result from a combination of risks. For example, the risk of low birth weight is signifi-

cantly increased by the co-existence of malaria infection and maternal anemia.[83] The children born to these mothers are also at risk of fetal anemia.[77] Research has shown that impairment can be experienced by the whole range of low birth weight children (<750g – 2500g).[92,93] Whilst the initial impairments may be undetectable, these children may lack the resilience needed to overcome latter adversity.

Summary

Malaria infection most commonly leads to impairments in physical growth, movement-related functions, and mental functions. Other outcomes which have been observed are impairments of the voice and speech, reproductive functions, sensory functions, immunological systems and the structure of the eye. For the direct pathways, the further to the right in Figure 2 you move the more severe the infection, the more potential pathways to impairment exist and the greater the risk of more severe outcome. However fewer children are implicated. This relationship does not hold for the indirect pathways. Little is known about the links to impairment through these pathways, but the implication is that a large proportion of the malaria exposed population is at risk of impaired development through one or a combination of these pathways.

Discussion

In order to understand the true burden of malaria it is essential to include a calculation of the impact upon the growth and development of children who have been exposed to malaria infection. Exposure to malaria leads to impairment and disability, the effects of which extend beyond the time of infection.[2,3,23,24] We have been able to establish that in general, the more sick the child the higher the risk of developing more severe, longer term impairment.[22,24] Despite the differences in the assessment tools applied in the reported studies, the application of the ICF has helped to summarize results across different contexts, and to clarify which functional areas are more commonly implicated.

What should we be measuring?

All the potential pathways described require further clarification before we can calculate either the severity of the burden or the numbers of individuals implicated. Investigations to date have concentrated on those children who have experienced cerebral malaria and are therefore at risk of the most severe impairment. Whilst the potential severity of the outcome supports the importance of more detailed investigations of this pathway, the total number of affected children is relatively small (1-2% of the child population in a malaria endemic area suffers from this form of the disease).[94]

The other pathways described involve a far greater proportion of the population. The most important in terms of numbers is parasitization, where 100% of children in endemic areas are affected. However, the effects of the parasitization may be negligible,[8] or, as suggested by the experience of macro-parasitic infections, readily reversible.[95]

There is also a potential burden felt by the child who is not ill. Since this burden is disproportionately felt by those with the lowest income,[96] it might be best characterized as due to poverty rather than malaria per se. However, as described by Sachs and Malaney[97] the two may be inextricably interlinked. The literature suggests that to adequately describe the relationship between malaria and malnutrition, and to plan appropriate interventions, account must be taken of the specific and possibly changing needs of a defined target population.[98-100] The absence of data on the longer-term effects on growth and development of this combination of risk factors needs to be addressed.

The consequence of pre-natal exposure to malaria is identified as another major priority for future research, firstly because of the potential size of the affected group.[101] The associated low birth weight may be a direct cause of impaired growth and development.[93] In addition, the growth retardation at this sensitive point in development may also predispose the child to adverse consequences following exposure to other risk factors.[102]

We have mainly been concerned with defining the burden. That is answering the question 'which health experience leads to which health outcome?' We have also suggested that a single malaria infection may not itself lead to impaired outcome, but may predispose the affected child to adverse sequelae following repeated exposure, particularly when that child is challenged with a number of health risks.[103] To test this hypothesis requires a longitudinal design.[104,105] The starting point for this analysis will need to be the first point at which the child may be exposed to malaria infection, *in-utero*.

How should we be measuring it?

To define with greater precision the severity of the impairment, and to calculate the long term burden on individuals, their families and the wider community, a number of methodological issues need to be addressed in future studies. The first issue concerns the selection of measurement tools applied, and the interpretation of results. The problem extends beyond needing more context-appropriate assessments.[106] Test developers need also to address the current limitation of neuropsychological assessment - that real life implications of impaired performance are seldom defined.[107] In this overview we were unable to apply the second tier of the ICF, Activity Limitations and Participation Restriction, because of the absence of this information in relation to malaria infection. Descriptions at this level of disability, and of real life outcomes, would help in defining the severity of the impairment observed, and in combining data across studies. Being able to define the meaning of impaired performance on tests of function in real life situations would also inform and guide support services in designing appropriate interventions.

Another limitation of the current literature is due to the cross-sectional design of the studies reported. Such studies can inform us as to the nature and extent of the burden at one age, or at one time point, post-infection. Child development is a dynamic process, and is best investigated in longitudinal studies.[108] A longitudinal perspective allows the description of changes in the burden as a child grows older, and is expected to play different roles in the family and community structure.[109] In some functional areas, it has been seen that the burden may decrease.[110] The Van Hensbroek study illustrated how even dramatic neurological impairments following cerebral malaria resolve over time, reducing the burden estimated by cross sectional data.[111,112] Other studies have suggested that the burden of severe disease may increase with time since insult. For example, in planning and organizational skills, which do not themselves mature until after the peak incidence period for severe disease, we might expect to find an increased burden as the child grows older.[24] Longitudinal data is needed to evaluate both the persistence of deficits (and thus the longer term burden), and to identify the most vulnerable.

It would be inaccurate to calculate the burden of malaria on child development without taking into account the large number of potential moderators influencing variability in outcome.[113] This variability has been associated with differences in socio-economic status and the presence of other infections and disease.[3]

Differences in outcome are also likely to be a consequence of the age at which the malaria infection occurs, and the age at which outcome is measured.[114] Understanding the sources of this variability clarifies the causes of impairment, and helps to identify the malaria attributable burden.[107,113] It also helps to identify those children most at risk of persistent deficits, as well as potential entry points for intervention. The statistical techniques which will allow us to either isolate the individual contribution of malaria or measure its effect in different combinations of risk, require large community-based samples, which have not always been available in previous malaria impairment studies.[115] The study of limited series, hospital-based samples may also have given us a distorted idea of who are the most vulnerable in the population. This is illustrated by the contradictory relationship between malaria and malnutrition seen in smaller, hospital- based studies compared to that found in larger, community-based studies.[43 46, 49]

Contradictory results may also reflect the different risk combinations encountered.[73,74] Indeed the multiple risk environments which characterize the lives of many children growing up in the malaria exposed world may make it very difficult, if not impossible, to isolate the malaria attributable proportion of observed impairments.[105] It may be more meaningful to identify common partnerships of risk factors and to calculate the combined burden.[103] A combination of different intervention strategies might also be expected to have an impact greater than the sum of their separate effects.[116] In this way interventions may be targeted at the most vulnerable.

The main conclusion that we draw from this overview is the complex interrelationship that exists between malaria infection and a large number of other risk factors, themselves associated with impaired growth and development. The presence of multiple risks, and the potentially changing relationship between those risks as a child matures, makes calculating a malaria attributable burden an extremely complex task. We suggest that it is not only more research that is required, but also a radical change in methodological approach. Only then will we be able to provide data that describe the severity of the burden in terms which are directly meaningful to the affected population, are comparable across populations, and show how the burden changes over time.

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Figure 1
Summary of the International Classification of Functioning, Disability and Health.[7]

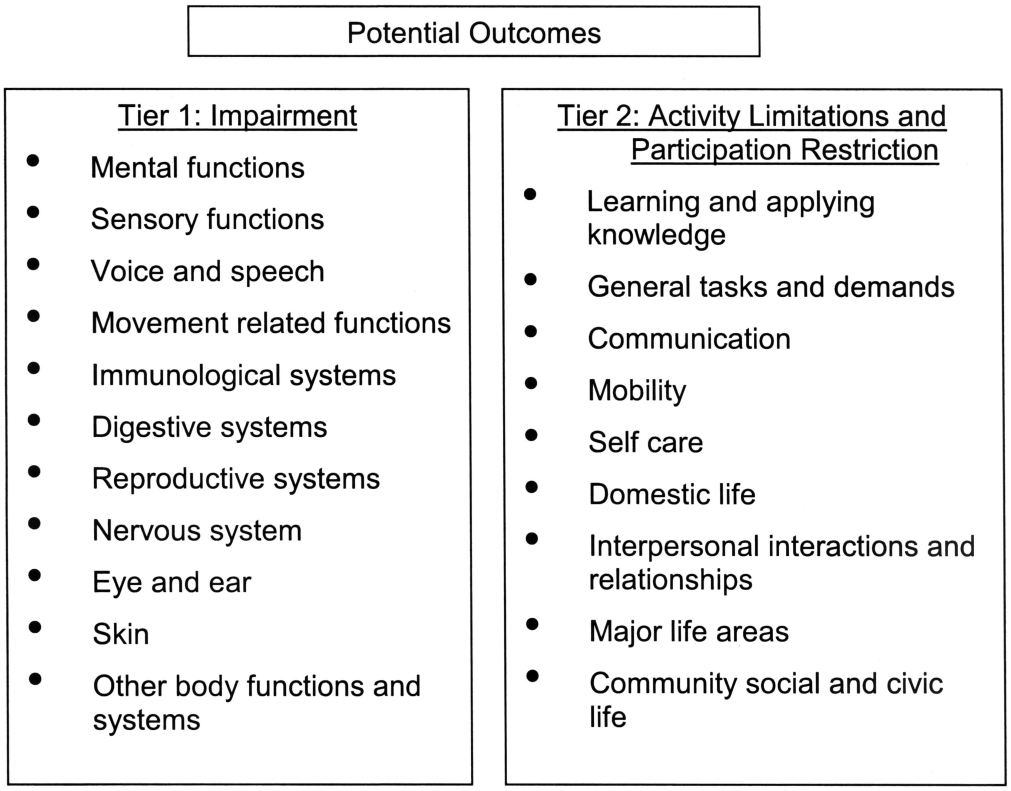
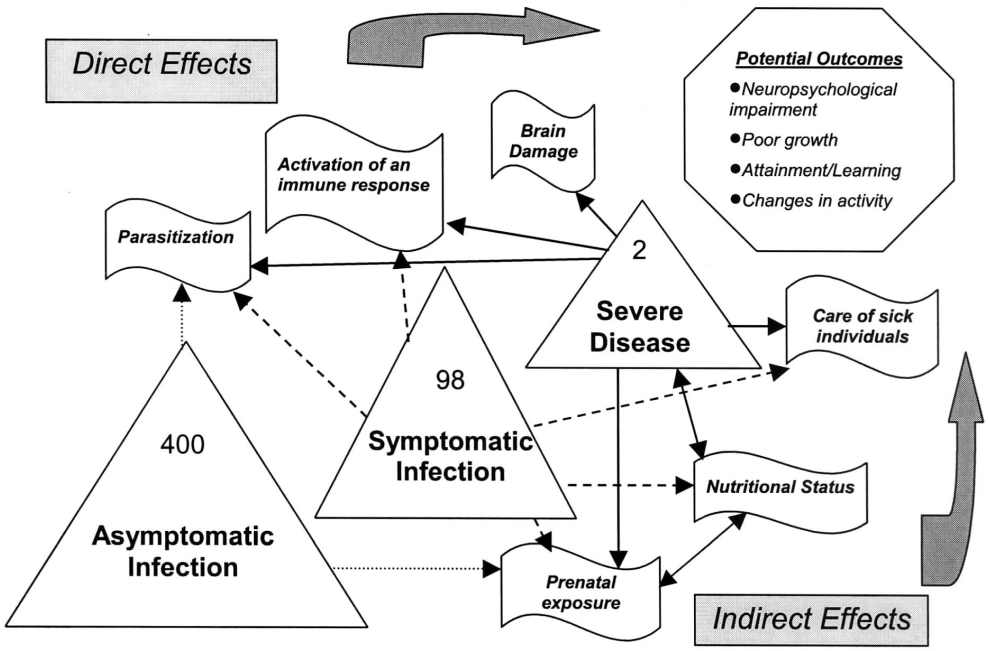


Figure 2
Direct and Indirect effects of malaria infection on child development.



Adapted from Holding & Snow[1]

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